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Cost-Effectiveness Analysis of Schizophrenia Relapse Prevention

An Economic Evaluation of the ZEUS (Ziprasidone-Extended-Use-In-Schizophrenia) Study in Spain

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Abstract

Objective: The aim of this study was to estimate the cost-effectiveness of schizophrenia relapse prevention in Spain using data from the ZEUS (Ziprasidone-Extended-Use-in-Schizophrenia) study.

Methods: Treatment of schizophrenia was modeled over 1 year using a retrospective deterministic model from the Spanish National Health System (NHS) perspective (year 2005). The primary outcome was the probability of relapse occurring within a 52-week period of treatment with daily doses of ziprasidone 40–160mg versus placebo. Data were obtained from a randomised, double-blind clinical trial (n = 218 patients). Antipsychotic cost, concomitant medications to treat adverse events (for example extrapyramidal symptoms) and medical costs associated with adverse events were derived from the clinical trial results and a Spanish health cost database. The average cost of a relapse admitted to hospital in Spain (€3421) was obtained from a retrospective study.

Results: The probability of psychosis relapse was 0.77 with placebo, and 0.43, 0.35, 0.36 and 0.38 with ziprasidone daily doses of 40, 80, 160mg and average dose, respectively ($p < 0.01$ vs placebo in all cases). The average annual incremental cost per relapse avoided was €186 for the average dose, ranging from a saving of €557 (80 mg/day) to an incremental cost of €1015 (160 mg/day), and was lower in all cases than the minimum cost of a relapse (€2830).

Conclusions: According to this evaluation, psychosis relapse prevention with ziprasidone is cost effective compared with no treatment from the Spanish NHS perspective. Ziprasidone therapy avoids a considerable number of relapses at a reasonable cost, producing cost savings.

Introduction

Clinically, and from the care perspective as well, schizophrenia is a challenging psychiatric disorder not only for the patient who endures it, but also for the patient's family and the persons responsible for the patient's care.[1] It is also associated with high morbidity and mortality rates compared with other chronic diseases. Schizophrenia is a severe psychotic disorder, with a prevalence that varies according to studies, but which is usually estimated at being approximately 1% of the adult population.[1-4] The natural history of the disease consists basically of three phases: acute phase (onset of severe symptoms), stabilisation phase and stable phase.[2] The characteristic symptoms of schizophrenia are usually classified into two groups: positive symptoms (hallucinations, delusions) and negative or deficit symptoms (emotional flatness, apathy). These clinical features are often associated with an inability to work and problems of social adaptation.[3,5] In addition, one of the major problems associated with treatment of the schizophrenic patient is the difficulty in ensuring follow-up and compliance with antipsychotic treatment. Discontinuation of treatment for any reason is associated with a recurrence of symptoms leading to a relapse, which frequently requires the admission of the patient to a psychiatric unit, with consequent deterioration in control of the disease, negative impact on the family and economic consequences for society resulting from the cost of hospitalisation and psychiatric internment.[6-10]

According to the Consensus of Experts of the Spanish Society of Psychiatry and the recommendations of the American Psychiatric Association, pharmacological treatment of the acute psychotic episode should be carried out with atypical antipsychotics (such as ziprasidone, risperidone, clozapine or olanzapine) or high-potency conventional (typical) antipsychotics (such as haloperidol).[3,11] Ziprasidone is an atypical antipsychotic with a high serotonin/ dopamine receptor affinity that has been shown to be effective and safe for the treatment of schizophrenia and for prevention of relapses of this disorder.[12,13]

Schizophrenia is one of the main components of healthcare expenditure in developed countries, accounting for 1.9% of the total healthcare budget in European countries and 2.5% in the US. In most countries, direct medical costs (hospitalisations, medication, etc.) represent one-third of the total cost of the disease,[5,14] and schizophrenic patients may occupy up to 20–25% of all available beds in psychiatric hospitals and 40% of all days of stay in these hospitals.[15,16] A 1998 study estimated that the annual direct medical costs of schizophrenia in Spain for a population of approximately 275 000 patients would be more than €667 million.[17] According to an economic study conducted in 1994, the annual cost of schizophrenic patients was €7395 per patient in the first year after diagnosis, €5561 in the second year (75.2%) and €4000 in the third year (54.1%).[18] Direct costs represented 47%, 35% and 43% of total costs, respectively. Informal care accounted for 36%, 40% and 42% of total costs, respectively. Finally, indirect costs, mostly from loss of productivity by the patients, amounted to 16%, 24% and 14%, respectively, in each of the first 3 years.[18,19]

The progressive growth of healthcare and pharmaceutical expenditure is mainly a result of aging of the population, an increase in the standard of living and the availability of new drugs. For this reason, in addition to the unquestionable role of the efficacy of antipsychotics, it is currently considered important to determine both the effectiveness under conditions of usual care (such as with the CATIE [Clinical Antipsychotic Trials in Intervention Effectiveness] study)[20] and, particularly, the efficiency (i.e. the cost per unit of effectiveness or cost effectiveness) of medicines.[21] This interest has also been manifested in Spain in the field of psychiatry, and specifically in the treatment of schizophrenia.[18,19,22-24] With regard to this, it seems logical to develop therapeutic recommendations aimed at optimising healthcare resource utilisation in the area of psychiatry, particularly in the treatment of schizophrenia. Relapse of this disease requires hospitalisation, which has a considerable cost for society. Prevention of relapse would free economic resources for

other healthcare items, leading to greater healthcare efficiency.[7,20,25,26] Therefore, the objective of the present study was to estimate the cost effectiveness of schizophrenia relapse prevention in Spain using data from the ZEUS (Ziprasidone-Extended-Use-in-Schizophrenia) study.[13]

Methods

Pharmacoeconomic Model

The study consisted of the development of a pharmacoeconomic model, a theoretical framework that allows simulations to be made of complex healthcare processes related to drugs, and which is constructed according to pre-established protocol using estimations obtained from available data (published or not) on efficacy, toxicity and costs of the alternatives compared. Simulations were performed using a deterministic model built in Microsoft Excel.[27]

Target Population

This is the hypothetical patient group in which the theoretical analysis is performed and therefore the population to which the results of the study are applied. The target population was Spanish adult patients with stable chronic schizophrenia.

Premises of the Model

The premises considered in the model are discussed below and summarised in table I.

Estimation of Efficacy

The type of pharmacoeconomic analysis that should be performed depends on whether differences in efficacy or toxicity exist between the treatments. In this analysis, the results of the ZEUS study were used; a 52-week, randomised, double-blind, placebo-controlled clinical trial assessing the efficacy of ziprasidone (in daily doses of 40mg [n = 75], 80mg [n = 72] or 160mg [n = 71]) versus placebo (n = 75) in the prevention of schizophrenia relapses.[13] The primary endpoints were rate of relapse and relapse-free time, calculated using survival analysis from the number of relapses observed with each intervention. The rate of relapse was used to calculate the probability and risk of relapse in a given period using an actuarial analysis. Ziprasidone, at any of the daily doses used in the study, significantly reduced the cumulative rate of relapse compared with placebo, with no significant differences between the doses of the active drug. Probabilities of relapse requiring hospitalisation were 0.43, 0.35, 0.36 and 0.38 for the 40, 80 and 160 mg/day dosages and the average dosage (base case), respectively ($p < 0.001$ in all cases, except for the 40 mg/day dosage, with $p < 0.003$), versus a probability of 0.77 with placebo (table II). Given that there were statistically significant differences in efficacy between ziprasi- done and placebo, a cost-effectiveness analysis was performed.

The minimum cost reported in the Psychosp study (lower limit of 95% CI) for relapse requiring hospitalisation was €2830.29.[25] In the model, we considered that treatment with ziprasidone could be cost effective provided that the cost to prevent one relapse of psychosis was lower than the cost indicated for an episode of relapse. Finally, the model estimated the number of patients who would need to be treated (NNT; the inverse of the absolute risk reduction) with each of the ziprasidone dosages to prevent one relapse of psychosis.[28] The NNT to observe one relapse was also estimated for each treatment.

Timeframe

This economic evaluation used the probabilities of relapse over 1 year in patients treated with ziprasidone or placebo (no treatment) obtained in the ZEUS clinical trial.[13]

Perspective of the Analysis

The evaluation was performed from the Spanish National Health System (NHS) perspective, and therefore only direct healthcare costs related to treatment of schizophrenia were included.

Estimation of Costs

The following costs were included in the analysis: (i) acquisition cost of drugs; (ii) cost of concomitant medications for treatment of symptoms associated with underlying disease; (iii) cost of treatment

Table I. Summary of main premises and estimations considered in the pharmacoeconomic model of schizophrenia relapse prevention with ziprasidone (ZIP) vs placebo

Item	Estimations, premises	Reference
1. Probability of relapse requiring hospitalisation during treatment with ZIP or placebo	40 mg/day: 0.43 80 mg/day: 0.35 160 mg/day: 0.36 Average dose: 0.38 Placebo: 0.77 (See table II)	12
2. Timeframe of analysis	1 year (52 weeks)	
3. Perspective of analysis	Spanish National Health System perspective	
4. Daily costs of treatment with ZIP (RP + VAT)	40 mg/day: €4.86 80 mg/day: €4.96 160 mg/day: €7.40 240 mg/day: €11.10	27
5. Percentage of patients by no. of days of treatment with ZIP in 1 year	365 days: 42.7% 270 days: 4.9% 180 days: 22.8% 120 days: 29.6%	12
6. Percentage of patients who took concomitant medications, and daily cost	See table III	12
7. Percentage of patients with AEs related to ZIP by resource utilisation	See table IV	12
8. Resource utilisation because of AEs	Mild to moderate AE: no associated cost Severe AE: one unscheduled visit to psychiatrist Serious AE: one visit to emergency department Laboratory AE: one additional determination	Estimate
9. Cost of psychiatric visit [mean (minimum–maximum)]	€62.10 (€49.68–€74.52)	28
10. Cost of visit to emergency department [mean (minimum–maximum)]	€107.90 (€86.32–€129.48)	28
11. Cost of hospitalisation in psychiatric ward per relapse [mean (minimum–maximum)]	€3.421.28 (€2.830.29–€3.842.50)	23
12. Cost of a laboratory determination (blood, urine, biochemistry and liver function) [mean (minimum–maximum)]	€39.70 (€31.76–€47.64)	28
13. Cost of ECG [mean (minimum–maximum)]	€18.60 (€14.88–€22.32)	28
14. Hospitalisation for relapse in psychiatric ward	Assumed to occur 12 weeks after the start of treatment	Estimate
15. Mean hospital stay per relapse [mean (minimum–maximum)]	21.78 days (19.05–24.50) days	23

AEs = adverse events; **RP + VAT** = retail price plus 4% value added tax.

of adverse events (AEs) related to the study medication; and (iv) cost of schizophrenia relapse requiring hospitalisation. The following costs were not included: direct healthcare costs resulting from consumption of resources scheduled in the clinical trial (as they were considered equivalent for all treatments), costs of rescue medication (antipsychotics administered to patients who initially received placebo and withdrew from the study), direct non-healthcare costs (transportation, child care, etc.), indirect costs resulting from absenteeism from work, or intangible costs caused by suffering as a result of the disease.

The total cost of treatment with ziprasidone was calculated by multiplying the daily cost of each dose (or the weighted cost in the case of the overall analysis of the base case) by the estimated number of days the patients received treatment in the ZEUS study (table I). Patients who experienced a relapse were considered to have discontinued the prescribed treatment, and the cost of treatment was not considered from that time on. Similarly, the cost of treat-

Table II. Efficacy results of the ZEUS (Ziprasidone-Extended-Use-In-Schizophrenia) clinical trial: cumulative incidence and probability of schizophrenia relapse with ziprasidone vs placebo at 52 weeks of treatment[12]

Group	n	Cumulative incidence at 52 weeks (%)	Probability of relapse at 52 weeks	p-Value vs placebo
Placebo	75	61	0.77	
Ziprasidone 40 mg/day	75	38	0.43	0.003
Ziprasidone 80 mg/day	72	31	0.35	0.001
Ziprasidone 160 mg/day	71	34	0.36	0.001
Ziprasidone weighted dose	218	34	0.38	0.001

ment was not considered from the time a patient withdrew as a result of an AE. The mean number of days of treatment and the proportion of patients in each category was calculated from the incidence of AEs and the survival curves observed in the ZEUS study (table I). The cost of concomitant medication required for treatment of symptoms associated with underlying disease, such as agitation, insomnia, nervousness and extrapyramidal symptoms, was also obtained from the ZEUS study in which lorazepam, biperidine and propranolol were administered in the proportions and with the daily costs indicated in table III. The cost of treatment of AEs related to ziprasidone was estimated based on the following assumptions: (i) mild or moderate AEs do not have associated costs; (ii) severe AEs cause an unscheduled visit to the psychiatrist; (iii) serious AEs cause at least one visit to an emergency department; (iv) abnormal laboratory test values generate an additional blood and urine determination, biochemistry test and liver function test. The AE occurrence rate observed in the ZEUS study is summarised in table IV. Finally, it was considered that relapses of psychosis requiring hospitalisation (hospital stay of ≥24 hours) had an average cost per relapse equal to that obtained in the Psychosp study (€3421), which corresponds to a mean hospital stay of 21.78 days, with a daily cost of €157 (table I).[25]

All unit costs included in the model are expressed in 2005 euros. Drug acquisition costs were obtained from the database of proprietary medicinal products of the Spanish Board of Pharmacy and costs of other healthcare resources were obtained from a Spanish health cost database (tables I and III).[29,30]

Guidelines Followed

This study was conducted in accordance with the general guidelines for performing pharmacoeconomic analyses in Spain,[31] the guidelines published by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA),[32] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practice Modeling Principles.[33]

Sensitivity Analysis

The estimations considered under the previous headings constituted the base case of the study (using the average values for the ziprasidone doses, resource costs and probabilities of relapse). To verify the stability of the results and the consistency of the estimations made, simple univariant sensitivity

Table III. Percentage of patients who took concomitant medication in the ZEUS (Ziprasidone-Extended-Use-In-Schizophrenia) study and average daily costs (ADC)[12]

Group	Lorazepam (%)	Biperidine (%)	Propranolol (%)	ADC (€)[a]
Placebo	66.66	13.33	1.33	0.09
Ziprasidone 40 mg/day	60.53	15.79	5.26	0.07
Ziprasidone 80 mg/day	54.17	12.50	1.38	0.09
Ziprasidone 160 mg/day	57.75	19.72	2.82	0.08
Ziprasidone weighted dose	57.52	15.98	3.18	0.08

a Retail prices plus value added tax.

Table IV. Proportion of patients with adverse events (AEs) in the ZEUS (Ziprasidone-Extended-Use-In-Schizophrenia) study and resource utilisation (additional laboratory determinations and ECG)[12]

Group	Serious AEs (%)	Severe AEs (%)	Additional laboratory determination (%)	ECG (%)
Placebo	0.00	9.33	25.35	10.67
Ziprasidone 40 mg/day	3.95	13.16	29.73	11.84
Ziprasidone 80 mg/day	0.00	6.94	28.57	13.89
Ziprasidone 160 mg/day	0.00	2.82	54.29	7.04
Ziprasidone overall	1.36	7.74	37.35	10.95

analyses were performed in which the following scenarios of treatment with ziprasidone versus no treatment were considered: (i) different dosages of ziprasidone (40, 80, 160 and 240 mg/day); (ii) minimum and maximum unit costs of the healthcare resources (± 20%); (iii) estimated threshold level of the theoretical probability of relapse with ziprasidone at which the annual cost of preventing a relapse would be equal to the minimum cost reported for relapse in the Psychosp study (lower limit of 95% CI: €2830);[25] (iv) estimated threshold number of days of hospital stay at which the cost of preventing a relapse would be equal to 0; and, finally, (vi) estimated indirect costs (resulting from absenteeism from work) that would be avoided with ziprasidone by reducing hospitalisations versus placebo.

Results

Number Needed to Treat

The NNT (95% CI) to prevent one relapse of schizophrenia with ziprasidone 40, 80, 160 mg/day or average dose versus placebo was 2.9 (1.8, 3.1), 2.3 (2.2, 4.2), 2.4 (2.1, 4.0) and 2.6 (2.0, 3.7), respectively (table V). The NNT to observe one relapse was 2.3. 2.9. 2.8 and 2.6 for the respective dosages of ziprasidone and 1.3 patients in the placebo group (table V).

Cost Analysis

The approximate annual cost per patient treated with ziprasidone 40, 80, 160 mg/day and the average dose was €2724, €2446, €3100 and €2754, respectively, compared with €2682 per patient in the placebo group. In other words, the incremental costs produced with ziprasidone were €42, €−236 (savings), €418 and €72, respectively. These results occurred in spite of the additional acquisition cost of ziprasidone, mainly because the annual cost per relapse was much higher in untreated patients (€2634) than in patients treated with ziprasidone (approximately €1183–€1471) [table VI].

Cost-Effectiveness Analysis

The average annual incremental cost per relapse was €186 for the average dose of ziprasidone, ranging from approximately €−557 (savings) for the 80 mg/day dosage to €1015 for the 160 mg/day dosage. These values were lower in all cases than the average cost of a relapse (€3421) and consequently also lower than the minimum cost of a

Table V. Number needed to treat (NNT) to prevent one schizophrenia relapse and to observe one schizophrenia relapse

Group	n	NNT to prevent one relapse (95% CI)	NNT to observe one relapse (95% CI)
Placebo	75		1.3 (1.2, 1.4)
Ziprasidone 40 mg/day	75	2.9 (1.8, 3.1)	2.3 (2.0, 2.8)
Ziprasidone 80 mg/day	72	2.3 (2.2, 4.2)	2.9 (2.4, 3.7)
Ziprasidone 160 mg/day	71	2.4 (2.1, 4.0)	2.8 (2.3, 3.5)
Ziprasidone weighted dose[a]	218	2.6 (2.0, 3.7)	2.6 (2.2, 3.3)

a Base case.

Table VI. Results of pharmacoeconomic analysis of schizophrenia relapse prevention with ziprasidone vs placebo. Base case and sensitivity analysis by daily dose of ziprasidone

Group	n	Annual costs per patient (€)					Annual cost per relapse avoided (€)
		primary treatment	concomitant medication	adverse events	relapse	total	
Placebo	75	0.00	29.83	17.84	2634.39	2682.06	
Ziprasidone 40 mg/day	75	1193.83	33.04	26.44	1471.15	2724.48	124.74
Ziprasidone 80 mg/day	72	1218.40	25.64	18.24	1183.76	2446.04	–556.63
Ziprasidone 160 mg/day	71	1817.77	32.91	24.61	1224.82	3100.11	1014.70
Ziprasidone weighted dose[a]	218	1405.16	30.55	23.14	1296.01	2754.86	186.09

a Base case.

relapse (€2830), considered as the threshold value for establishing the cost effectiveness of treatment with ziprasidone (table VI).

Sensitivity Analysis

The daily dose of ziprasidone did not determine the annual cost per relapse avoided in a uniform manner because a relationship was not found between the dose administered and the efficacy of ziprasidone in preventing psychosis relapse. This led to diverse results being obtained, such as those previously indicated (table VI). The 240 mg/day dosage of ziprasidone is not approved in Spain, but is sometimes used in patients who do not respond to lower doses. In this case, the annual cost to prevent a relapse would be approximately €3221, a cost higher than the minimum but lower than the average cost of a psychosis relapse (table VII).

Application of the minimum and maximum healthcare costs (table I) also results in large variations in the outcome of the base case, with annual costs per relapse avoided of approximately €–234 (savings) and €606, respectively (table VII). The probabilities of relapse with ziprasidone ranged from 0.35 to 0.43, based on the doses administered in the ZEUS clinical trial.[12] For the cost of preventing a relapse to be equal to the minimum cost of a relapse (€2830) reported in the Psychosp study,[25] the theoretical probability of relapse with ziprasidone would have to increase to 0.54 (figure 1), a figure much higher (11–19%) than actual efficacy results observed for ziprasidone in the clinical trial.

On the other hand, the probability of relapse with ziprasidone obtained in the base case was 0.379 (ZEUS study);[12] if the probability of relapse of psychosis decreased to 0.357, additional costs would also not be produced for treatment with ziprasidone versus placebo.

In the base case, an average hospital stay per relapse of 21.78 days was considered, with a daily cost of €157; if the duration of the average stay increased (with the same daily cost) to 22.96 days, the additional cost of treatment with ziprasidone would be virtually zero compared with placebo. Considering 10 and 30 days as the hypothetical extreme values of hospital stay per relapse of psychosis, the cost per relapse avoided with ziprasidone would range from €2036 to a saving of €1105, respectively (figure 2).

Finally, the indirect costs (resulting from absenteeism from work) that would be avoided with ziprasidone by reducing the number of hospitalisations versus placebo were estimated. It was determined that the annual savings with ziprasidone would be €71 per patient.

Table VII. Additional sensitivity analyses of the pharmacoeconomic model of schizophrenia relapse prevention with ziprasidone vs placebo

Analysis	Annual cost per relapse avoided (€)
Base case	186.09
Ziprasidone 240 mg/day	3220.74
Minimum costs of healthcare resources	–233.87
Maximum costs of healthcare resources	605.81

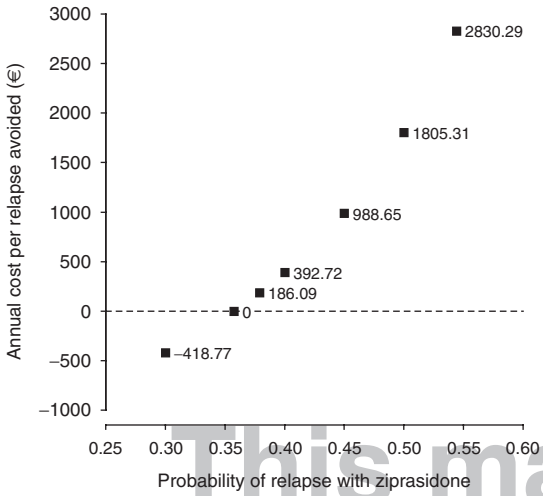

Fig. 1. Annual cost (€2005) per relapse avoided for the different theoretical probabilities of relapse with ziprasidone. The probabilities of relapse with ziprasidone ranged from 0.35 to 0.43 in the ZEUS (Ziprasidone-Extended-Use-In-Schizophrenia) trial.[13] For the cost of preventing a relapse to be equal to the minimum cost of a relapse (€2830), the theoretical probability of relapse with ziprasidone would have to increase to 0.54.

Discussion

Based on the results obtained with the present model, prevention of schizophrenia relapse with ziprasidone is cost effective compared with the option of no preventive treatment. The sensitivity analyses indicated that the base case of the analysis was stable since treatment with ziprasidone could be considered cost effective in the majority of the scenarios as the cost of preventing relapse of psychosis was lower than the cost of an episode of relapse. The exception was observed when the 240 mg/day dosage of ziprasidone was included in the model as preventive treatment for schizophrenia relapse, in which case the cost of preventing a relapse would be higher than the minimum cost of treatment of a relapse, although lower than the average cost observed in the Psychosp study.[25] In this regard, it should be pointed out that, from a strictly pharmacoeconomic point of view, it is recommended that the assumptions made in the base case of the sensitivity analysis be varied, and that this dosage of the drug is outside the dose range recommended in the prescribing information for ziprasidone.[13] Furthermore, the sensitivity analysis only included the cost of this dosage and did not vary the probability of relapse expected with this dosage, which is unknown since it has not yet been explored.

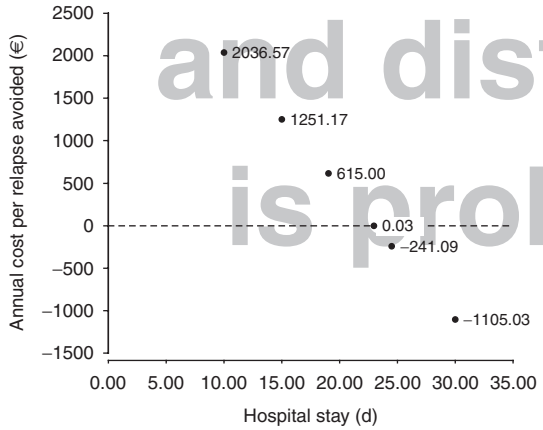

Fig. 2. Annual cost (€2005) per relapse avoided with ziprasidone for different durations of hospital stay for psychosis relapse.

However, it should be taken into account that the base case showed large quantitative variations in relation to factors such as the probabilities of relapse with the different doses, the extreme healthcare costs and the duration of hospital stay for relapse. Thus, the best and worst cases for ziprasidone would produce an annual saving of approximately €500 or incremental cost of approximately €1000 for the NHS per relapse avoided, respectively, which in all cases was lower than the cost of hospitalisation for relapse of schizophrenic symptoms. Since the cost of hospitalisation is the most important component in the cost of schizophrenic relapse, it is worth noting that when duration of hospital stay and hence the cost of hospitalisation were modified, not only were the conclusions of the model modified, but stays of ≥22.96 days showed savings for the NHS when ziprasidone was used as the preventive agent for relapse. Furthermore, the cost per relapse avoided continued to be lower than the cost of relapse when duration of stay was reduced to within the 95% CI observed for this variable in the Psychosp study.[25]

An aspect that should be noted, although not considered in the main analysis, is the impact of

hospitalisations caused by psychosis relapses on lost work days. Compared with the option of no treatment, the annual savings with ziprasidone would be approximately €71 per patient. This value, which could be considered modest in magnitude, was calculated from the value of the minimum wage and so may have underestimated the real impact in terms of lost work productivity.

We did not find similar economic evaluations in our setting to allow us to perform a comparative analysis or at least to check whether the results found in our evaluation are consistent with the existing scientific literature. In a systematic review in the UK published in Health Technology Assessment in 2003, the cost per quality adjusted life-year (QALY) gained with first-line treatment with ziprasidone was £1415 compared with sertindole (2003 values).[34] A more recent pharmacoeconomic model developed in Germany that compared the cost effectiveness of treating schizophrenia with ziprasidone, haloperidol, risperidone and olanzapine, concluded that ziprasidone was the most cost-effective drug, with costs for symptom control during 1 month of €2370, €3054, €2456 and €2514, respectively.[35] Similar results to the previous study were found by Bobes et al. using an economic model with Spanish costs.[24] These studies are not comparable with the present model since they did not consider the option of not treating the disease. Although various reviews and studies have been carried out on the pharmacoeconomic profile of first- and second-generation antipsychotics,[36-38] the only study comparable to ours is the one by Osterheider et al.,[39] who also found that prevention of schizophrenia relapse with antipsychotics was cost effective. However, there does seem to be a consensus among the different authors as well as the previously mentioned reviews that schizophrenic relapse is one of the determining factors in the greater costs of treating schizophrenia and that treatment strategies for this psychiatric disorder, in addition to clinical objectives, should be aimed at preventing psychosis relapse in view of the cost effectiveness shown in this and other studies.[36-41]

Study Limitations

Assessment of these results should take into account a series of limitations of the study. Firstly, it is a theoretical model (which by definition is a simplified simulation of reality) based on a nonpragmatic clinical trial, and its results should therefore be considered as estimations for a typical patient, which may be useful as a tool for clinical decision making.[26] Secondly, it should be considered that a dose-dependent relationship was not established for the efficacy of ziprasidone, which makes interpretation of the results difficult since the daily dose is an important determining factor in the final cost of the disease. On the other hand, the long duration of the ZEUS clinical trial (52 weeks), unusual in studies in the field of schizophrenia, and the fact that both utilisation of resources and their unit costs were obtained from Spanish studies and sources, supports the relevance of the results for clinical practice in Spain.[25,29,30]

To attempt to minimise the limitations of the model, conservative estimates (and averages) were used and a sensitivity analysis was performed considering various extreme scenarios. The major cost determinants in the cost of prevention were the dose of ziprasidone used and the cost of hospitalisation. The latter was determined by its duration. In our evaluation, we had to vary the dosage and its cost up to a maximum of 240 mg/day without varying efficacy, a dosage which, although sometimes used in specific patients, is outside the recommended dose range, as previously indicated. This provides additional support for the cost-effectiveness profile shown by this drug. The duration of hospitalisation, another major cost component, was obtained from a study conducted in our setting, in which a mean stay of approximately 22 days was observed.[25] Although this duration may be variable, the scientific literature supports similar or even higher values than those used in this evaluation (it should be remembered in this regard that the cost-effectiveness profile of ziprasidone improves with increasing duration of hospital stay).[7,22,40]

Conclusion

Taking into account the previously mentioned limitations, it can be concluded that prevention of schizophrenia relapse with ziprasidone is cost effective compared with no treatment from the Spanish NHS perspective. Treatment of patients with stable chronic schizophrenia prevents a considerable number of relapses at a reasonable cost and produces cost savings.

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